Perspective on the "Animal Rule"

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Efficacy Issues for Counter Terrorism (CT) Products

- **In some cases, human efficacy trials may not be feasible nor ethical**
  - ☑ **Epidemiology precludes "field trials", the usual source of efficacy data, and**
  - ☑ **Cannot conduct human challenge/protection studies**

Animal Rule

- **New Drug and Biological Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible. Federal Register 67: 37988-37998, May 31, 2002. (Final Rule)**
  - ☑ **21 CFR 601.90-95 (biologicals)**
  - ☑ **21 CFR 314.600-650 (drugs)**

Animal Rule

- **Drugs & biologicals that reduce or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances**

Animal Rule

- **FDA may approve a product for which**
  - ☑ **Safety has been established and**
  - ☑ **Requirements of Sec. 601.90 (314.600) met based on adequate and well-controlled animal trials when results of those animal studies establish that product reasonably likely to provide clinical benefit in humans**

Animal Rule

- **Rely on evidence from animal studies only where**
  - ☑ **Reasonably well understood**
    - **Mechanism of toxicity of agent**
    - **How product prevents the toxicity**
  - ☑ **Effect independently substantiated in >1 species (some exceptions)**
    - **Including species expected to react with a response predictive for humans**

Animal Rule

- **Animal study endpoint clearly related to desired benefit in humans**
  - ☑ **Generally, enhancement of survival or prevention of major morbidity**
- **Selection of an effective dose in humans**
  - ☑ **Kinetics & pharmacodynamics and/or other relevant data, in animals & humans**
- **Still need human clinical data**
  - ☑ **Safety**
  - ☑ **PK/immunogenicity data**

Animal Rule

Approval subject to three requirements

- **Postmarketing (PM) studies**
  - ☑ To verify and describe the product's clinical benefit when feasible & ethical (due diligence)
  - ☑ May not be feasible until an exigency arises
- **PM restrictions as needed to assure safe use, commensurate w/product specific safety concerns**
  - ☑ E.g., distribution restricted to certain facilities or health care providers with special training or experience, if needed

Animal Rule

Continued

Approval subject to three requirements

- **Labeling for recipients**
  - ☑ Provided prior to use
  - ☑ Explain that product's approval based on efficacy studies conducted in animals alone
  - ☑ Indication(s)
  - ☑ Directions for use (dosage & administration)
  - ☑ Contraindications
  - ☑ Adverse Events
  - ☑ Other relevant information

Animal Rule

- **Reasons to withdraw approval**
  - ☑ PM clinical study fails to verify clinical benefit
  - ☑ Applicant fails to perform PM study with due diligence
  - ☑ Experience shows that PM restrictions are inadequate to ensure safe use of the product
  - ☑ Applicant fails to adhere to PM restrictions
  - ☑ Promotional materials false or misleading, or
  - ☑ Other evidence demonstrates that product is not safe or effective

Animal Rule - Scope

- **Rule does not apply if product approval can be based on standards described elsewhere in FDA's regulations**
  - ☑ **e.g., accelerated approval based on human surrogate markers or clinical endpoints other than survival or irreversible morbidity**

Safety Data

Indication: Preventive vaccines for healthy persons

- Target populations
- How much is enough to support licensure?
- Thousands, ideally from randomized studies
- Data quality important
- Risk/benefit

Safety Evaluation

- Animal rule does not address safety evaluation of products to which it applies
- Safety discussed briefly in preamble to Rule
  - ☑ Use “preexisting requirements”
- Agency believes that, w/one limitation, safety of most of these products can be studied in volunteers similar to people who would be exposed to the product
- Limitation – may be inability to examine possible adverse interactions between toxic substance and new product

"Supplemental Clinical Studies" To Assess Safety (Prelicensure)

- **Small efficacy trials or other limitations**
  - ☑ **E.g., if efficacy assessed by comparative immunogenicity study(s) with several hundred per group (combination vaccines)**
  - ☑ **"Animal rule"**
- **Novel vaccine concepts**

Simultaneous Administration (SA)

- FDA's Guidance for Industry for Evaluation of Combination Vaccines (1997)
- Note: No previous FDA policy on this topic
- Licensed vaccines administered simultaneously w/the new vaccine:
  - ☑ Obtain immunogenicity & safety data to support SA if recommended schedule for new vaccine is same, or overlaps, with one or more licensed vaccines
  - ☑ Timing: Prelicensure

Standards of Licensure

- Safety
- Purity
- Potency
- Efficacy
- Stability
- cGMP Compliance

Vaccine Production/Quality Control

Common Principles

- Detailed manufacturing procedures: consistency of production
- Defined compatible components
- Product characterization: specifications
- Cell substrate; Adventititous agent testing
- Source (e.g., BSE)
- Examination for extraneous materials
- Stability

Implications of Final Rule for Drug Development

- Early/multiple discussions with FDA
- Detailed justification concerning why efficacy trials not feasible/ethical
  - ☑ Agency may not concur
  - ☑ Ability to perform "field trials" may change over time, e.g.,
    - Clinical endpoint efficacy trial for anthrax vaccine possible in 1950s/60s (US mill workers)*

*Brachman, et. al., 1962. Field evaluation of a human anthrax vaccine. Am J Public Health. 52:632-645

Implications - Drug Development

- Pilot efficacy studies in animals
- Pivotal animal efficacy studies
  - ☑ Prospective primary endpoint
  - ☑ Prospective statistical plan
  - ☑ GLP (21 CFR 58)
- Multiple interactions with FDA Advisory Committees
  - ☑ Prior to animal efficacy trials, for concurrence w/concepts, in some cases
  - ☑ Following Agency's BLA review

Assays in Vaccine Trials

Importance of:

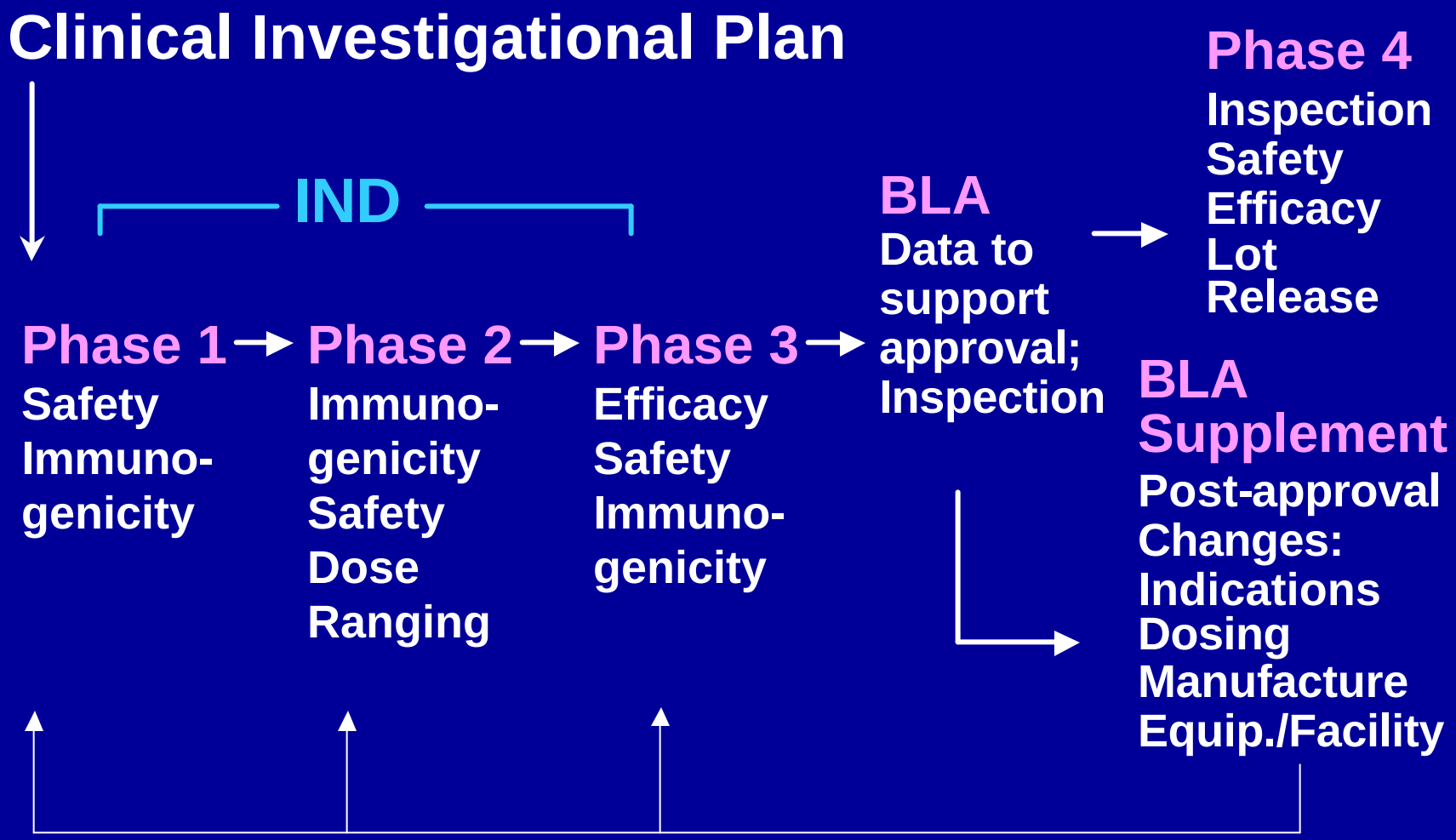
- **Assays to detect vaccine-elicited response(s)**
- **Assays to identify/characterize infections (immunologic, virologic)**
- **Considerable R & D can be necessary to develop and validate assays**

Assays in Vaccine Trials

Importance of:

- **Assay performance data**
  - ☑**Specificity, sensitivity, ruggedness, reproducibility, e.g., procedures to minimize false positive PCR**
  - ☑**Important for early trials**
  - ☑**Validation of assays before pivotal study**

Stages of Review and Regulation



IND =Investigational New Drug Application; BLA=Biologics License Application

Meetings with FDA (21 CFR 312.47)

Phase 1 → Phase 2 → Phase 3 → BLA

Pre-IND Meeting:

- Manufacturing Product
- Lot Release
- Animal safety & immunogenicity
- Phase 1 protocol

End-of-Phase 2 Meeting:

- Efficacy trial protocol(s)
- Phase 1/2 data
- Update** Product, etc.
- Rationale

Pre-BLA Meeting:

- Clinical data summary: S & E
- Update** Product, etc.
- Outline of BLA

BLA = Biologics License Application **Shouldn't be a surprise

Available Resources

Example of an FDA document:

- ☑ Guidance for industry - Content & format of chemistry, manufacturing & controls information & establishment description information for a vaccine or related product (1999)

Available Resources

- FDA documents/Federal Register notices/regulations
  - ☑ http://www.fda.gov/cber/publications.htm
  - ☑ 1-800-835-4709 or 301-827-1800
- International Conference on Harmonisation (ICH) documents
  - ☑ U.S., E.U. and Japan
- Anthrax Vaccines: Efficacy Testing and Surrogate Markers of Immunity Workshop - 4/23/2002 – Transcript on CBER internet

Conclusion - Product Development

- CT products present unique issues for clinical development
- Overall planning and coordination:
  - ☑ Product characterization/manufacturing
  - ☑ Early/frequent interaction with Agency, esp. if approval will be based on animal efficacy data
  - ☑ Anticipate future trials (e.g., critical assays)
  - ☑ Obtain sufficient safety, immunogenicity & efficacy data during development
- Utilize FDA documents & resources